Centocor

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03 December 2003

Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Draft Guidance for Industry – Comparability Protocols – Protein Drug Products and Biological Products – Chemistry, Manufacturing and Controls Information
[Docket No. 2003D-0385, 68 *Federal Register*, 52776-52777, 5 September 2003]

Dear Sir or Madam:

Centocor Inc., a member of the Johnson & Johnson family of companies, hereby provides comments on the Draft Guidance for Industry: Comparability Protocols – Protein Drug Products and Biological Products – Chemistry, Manufacturing and Controls Information.

We recognize the extensive effort that has gone into the preparation of the draft guidance. We appreciate the opportunity to comment on the guidance and are confident that our comments may enhance further revisions of the guidance.

The most significant comment pertains to Page 1, Line 30 of the guidance that states, "This guidance also applies to ...abbreviated new drug applications (ANDAs)..." We find this reference to ANDAs misleading and inappropriate, and we recommend that it be removed from this guidance.

The Federal, Food, Drug and Cosmetic Act provides under section § 505 (j), for the approval of generic drugs. This path allows the approval of generic drugs based upon an originator's preclinical and clinical data. It is not applicable to comparability testing for biological products. Including the statement about ANDAs in this guidance clearly but wrongly suggests that generic protein products and biologics may be approved under § 505 (j). In fact, no generic protein drug has ever been approved under this section of the statute because it was not intended to apply to biological products.

Furthermore, linking the relatively simple ANDA process that was designed for small molecules, to comparability protocols that are designed for complex biological products, ignores the complicated factors regarding the efficacy and safety associated with generic biological products, mainly the issue of immunogenicity. As the scientific community continues to discuss and debate such products, there is already general agreement that the simple ANDA process will not suffice for generic biologics making reference to ANDAs in this guidance inappropriate.

Additional comments on the draft guidance are provided in the attachment.

2003D-0385

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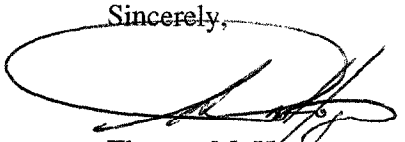
We appreciate the opportunity to provide comments on this guidance and are committed to collaborating with the Agency to develop improved versions of the guidance.

Please do not hesitate to contact me should you have any questions regarding these comments.

Sincerely,



Thomas M. Hogan
Senior Director, Worldwide Regulatory Affairs
Chemistry, Manufacturing and Controls

Attachments

cc: CDC

Centocor Inc.

Guidance For Industry - Comparability Protocols- Protein Drug Products and Biological Products - Chemistry, Manufacturing, and Controls Information

Draft Guidance – September 2003

Docket No. 03D-0385, CBER 200338

Comment Number	Line # of PDF Document Section/ Title	Comment/Recommendation for Revision	Comments regarding text
1.	Line 30 I. Introduction	Change from: "This guidance also applies to new drug applications (NDAs), abbreviated new drug applications (ANDAs), new animal drug applications (NADAs), abbreviated new drug applications (ANADAs), or supplements to these applications for protein drug products, and not sufficiently characterizable peptide products (e.g., complex mixtures of small peptides)." Change to: "This guidance also applies to new drug applications (NDAs), and new animal drug applications (NADAs), or supplements to these applications for protein drug products, and not sufficiently characterizable peptide products (e.g., complex mixtures of small peptides)."	Given that §505(j) of the Federal Food, Drug and Cosmetic Act, that prescribes the regulatory basis and process for ANDAs, was passed as part of the Hatch-Waxman amendments of 1984 expressly and solely to allow the approval of generic drugs by reference to an innovator's preclinical and clinical data, this statement in the guidance gives a strong implication that generic protein drugs and biological products can and will be submitted for approval under §505(j). In fact, no protein drug has ever been approved under this section of the statute, partly because the Hatch-Waxman law was structured such that it is not applicable to biological products, partly because there are many technical differences between these drugs and those produced by chemical synthesis that would render the approval of generic versions of proteins or other biologics under the §505(j) process unsafe. Therefore, we find the reference to ANDAs and the reference to ANDAs misleading and inappropriate and we recommend that they be removed.

Comment Number	Line # of PDF Document Section/ Title	Comment/Recommendation for Revision	Comments regarding text
2.	Lines 178-179 III. What To Consider… A. How Does a Comparability Protocol…	In some cases, a reduction of more than one reporting category may be possible (e.g., PAS to AR).	Please provide an example of when a reduction of more than one category is possible.
3.	Lines 272-275 III. What To Consider… C. When Might a Comparability Protocol be Inappropriate?	Delete lines 272-275 as currently stated: "A change in or move to a manufacturing site, facility, or area when a prior approval supplement is recommended because an inspection (e.g., a current good manufacturing practice (CGMP) inspection) is warranted (e.g., see examples in guidance listed in Section II.D.)" Insert a new paragraph: "When a Manufacturer moves a process to a manufacturing facility that has not been previously inspected, the approval of the Comparability Protocol signifies that the Manufacturer should notify the field that the facilities are ready for inspection. The inspection should be scheduled prior to the submission of the agreed data package to the review division. Upon receipt of the acceptable GMP status, the Manufacturer may implement the change without delay in accordance with the approved Comparability Protocol."	If a GMP inspection is warranted for a manufacturing site, facility, or area, it is not clear why the Comparability Protocol could not be submitted for the site change, and the Comparability Protocol be used to trigger the inspection. Since both a Comparability Protocol and a site change, which requires a GMP inspection must be submitted as a Prior Approval Supplement the Comparability Protocol should be the trigger for the GMP inspection. After the PAI and Comparability Protocol approval, the site change could be reported at the reduced reporting category without the need for the increased regulatory time constraints for implementation. As written, this represents a significant increase in the regulatory burden.
4.	Line 292 IV. Procedures For Comparability Protocols A. How should a Comparability Protocol Be Submitted?	For Clarification	Please clarify if formal FDA approval of the protocol is required prior to generating any data associated with the protocol or if generation of data may be initiated following agreement by the FDA and applicant during review of the protocol.

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5.	Lines 328-331 IV. Procedures For Comparability Protocols B. What If Study Results Do Not Meet the Criteria Specified in the Approved Comparability Protocol?	Current statement: "If you decide to pursue the change, we recommend that you submit a prior approval supplement that provides the supporting data to justify why the change will not adversely affect the identity, strength, quality, purity, and potency of the specific drug product as they may relate to the safety and effectiveness of the product." Add to the end: "Where the acceptance criteria for the change are not met, the change should be evaluated for impact on expected product. The results should be reported to FDA prior to formal submission of the data and reporting category determined following consultation with FDA."	Add a sentence to the end of the paragraph providing provision to allow for discussion if non-consequential acceptance criteria are not met. Provisions should be made that if the acceptance criteria are not met, it should not automatically bump the implemented change to a PAS. Also, where the Comparability Protocol criteria are not met, we recommend the use of the reporting category that would normally apply for the type of change instead of being required to submit a PAS. There should be some allowance for discussion with the FDA reviewer to determine if the missed acceptance criteria is of so little consequence that the original reporting category is still appropriate and can be maintained.
6.	Lines 610-611 E. Does FDA have Specific Concerns about Changing Manufacturing Facilities	General Comment.	Guidance should clearly state whether FDA would permit a supplement in a reporting category other than prior approval for a change to a new site which has not been inspected or does not have a satisfactory CGMP inspection.

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7.	Lines 662 V. Content Of A Comparability Protocol F. Can a Comparability Protocol Be Used for Container Closure System Changes?	For Clarification.	Please clarify the use of the word "repetitive" in line 662. Does this mean: A single change applied to numerous applications or a series of changes that have predefined acceptance criteria but which may extend beyond any single change?